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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
BERCH, MARK L	

ART UNIT	PAPER NUMBER
1624	

DATE MAILED: 03/16/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/603,503	NESTOR ET AL.	
	Examiner	Art Unit	
	Mark L. Berch	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 23-29 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 23-29 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 6/24/2003.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 23-29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Beauchamp.

Note Formula I in U.S.P. 5,043,339, since one of R and R^1 must be an amino acid, the genus describes basically mono- and diesters (depending on whether 1 or both of R, R^1 are amino acids). The preferred amino acids are listed at column. 2, lines 23 as glycine, alanine, valine, and isoleucine. This also happens to be the only amino acids used in the examples. Both mono and diesters are prepared; See Ex. 6. This than gives 8 choices; four monoesters and 4 diesters. There are 2 preferred choices for B, cytosine, and ganciclovir (column. 2, line 14). Again, these are the two bases of the examples. This then produces 8 X 2=genus of 16. The claims are limited to the HCl salt. 9 acids are named, including HCl. This constitutes a genus then of 16 x 9 = 144 compounds. A genus of that size renders all of the embraced species obvious. Note *Merck & Co vs. Biocraft*, 10 USPQ 2nd 1843, 1846 in which a reference disclosing "more than 1200 combinations", with no indication that any one of them was preferred over the others, was found to render each choice obvious. Note also *In re Corkill*, 226 USPQ 1005, 1008 and *In re Susi*, 169 USPQ 423, 425, with similar fact patterns.

With regard to the CMV of claims 25-26, note column 2, line 43 which states "particularly CMV", and human use appears on the same line, for claim 28. The oral administration of claims 24 and 27 is discussed in detail at column 4, lines 3-11.

With regard to the physical characteristics recited in claim 29, cannot be avoided simply by describing their compound in greater detail than the prior art. Otherwise, every obviousness rejection could be overcome, not with unexpected effect, but just by tacking on some trivial physical parameter, such as the temperature of a phase transition. In this regard, note that the MPEP addresses this issue. MPEP 2112 states: "A REJECTION UNDER 35 U.S.C. 102/103 CAN BE MADE WHEN THE PRIOR ART PRODUCT SEEMS TO BE IDENTICAL EXCEPT THAT THE PRIOR ART IS SILENT AS TO AN INHERENT CHARACTERISTIC" Note that this wording makes no mention of a burden to show that the characteristic (in this case, the two mentioned in claim 29) is likely to be present. All you have to show is that it's the same product, or even just seems to be the same product.

In the parent, paper of 8/13/02, page 12, applicants performed a calculation and arrived at a total of 486. While the reference possibly teaches a genus of that size, it also teaches a smaller genus. A reference is available for all that it teaches, see *In re Lamberti*, 192 USPQ 278, 280; *In re Boe,* 148 USPQ 507, 510; *In re Fracalossi*, 215 USPQ 569, 570. The fact that a reference teaches a genus A does not detract from a teaching of a subgenus A'. Specifically, while it is true that 9 amino acids are named, there is also a teaching of four preferred amino acids, at column 2, line 23. The fact that the broader list exists does not detract from the narrower list. It is not impermissible hindsight to

use a subgenus of 4 which the reference clearly labels as preferred. Use of the 4 instead of the 9 in this calculation gives a genus of 216.

In addition, the use of "3" (types of esters) in the third line is not believed to be correct. The reference describes two types of esters: the mono ester, and the diester. Thus, there is the mono glycine ester, the di-glycine ester, the mono-valine, the di-valine, etc. The use of the correct 2 in place of 3 will give the correct figure of 144. Applicants comments on page 13 are not agreed with in this regard. There is nothing in the reference to point to mixed esters. The method given in the reference would not make a mixed ester.

Applicants on page 14 of the same paper discussed some alleged "difficulties" in preparation. There does not appear to be anything there which is not already known to one of ordinary skill in the art of synthetic organic chemistry. Thus, applicants argued that the amino group of valine will have to be protected. Of course, but surely applicants are not arguing that one of ordinary skill in the art does not know how to prepare a valinate ester. Further, all these specific procedures may be the ideal method of making the mono-ester, but these are hardly essential. If one wishes the monoester rather than the dieter, one simply uses less than 2 moles, i.e. one mole of the esterifying agent. Indeed, even when one tries to make the bis ester, as was seen in example 6, one gets some of the mono-ester anyway. As page 6 notes, monovalinate was prepared, even if it were a "minor byproduct".

Further, this is a US Patent, and it says that it can make the mono- and the di-diesters. It is presumed to be correct (see 35 USC 282). It is of course possible that a US patent is actually in error. For the standard in such matters, cf. *In re Fracalossi*, 215

USPQ 569; *In re Weber*, 160 USPQ 549; *In re Lamberti*, 192 USPQ 278, 281; *In re Reid*, 84 USPQ 478; *In re Michalek*, 74 USPQ 107; *Ex parte Gray*, 10 USPQ2d 1922, 1928.

Further, even if it failed, the failure of a reference to provide a method of making is not necessarily fatal, so long as there is another method known prior to the relevant date. See *In re Sasse*, 207 USPQ 107; *In re Donohue*, 207 USPQ 196; *In re Donohue*, 226 USPQ 619. See also In re Samour 197 USPQ 1. And applicants have not argued that these could not be made but for methods of their own devising.

In the paper of 1/3/03 of the parent, applicants, citing an unnamed Federal Circuit decision state that there is no such rule that "regardless of how broad, a disclosure of a chemical genus renders obvious any species that happens to fall within it." Agreed, but the examiner has never made such an assertion. What the examiner has said, and applicants have not disputed, is that when a genus is sufficiently small, it does indeed render all of the species in it obvious. That is precisely what occurred in *Merck & Co vs. Biocraft*, 10 USPQ 2nd 1843, 1846 in which a reference disclosing "more than 1200 combinations", with no indication that any one of them was preferred over the others, was found to render each choice obvious.

The question, then, is whether this genus is sufficiently small. Applicants had calculated a genus of 486. In this paper, applicants did a new calculation and arrive at 648. However, using either of these numbers, this is still below the 1200. Applicants have presented no reasoning why a genus of "more than 1200 combinations" in *Merck* would render each choice obvious, and yet a substantially smaller number would not render each choice obvious in this case. Similarly, in *In re Corkill*, 226 USPQ 1005, 1008, there was a selection made "from among 'thousands' of compounds" and yet it

was still held obvious. Likewise, in *In re Susi*, 169 USPQ 423, 425, the court noted of the Lauerer reference used, "As appellant points out, Lauerer's disclosure is huge....." And still, obviousness was found to be present.

Moreover, even if the genus of 486 and the one of 648 is too large, a reference is available for all that it teaches, see *In re Lamberti*, 192 USPQ 278, 280; *In re Boe*, 148 USPQ 507, 510; *In re Fracalossi*, 215 USPQ 569, 570. There is also the genus of 144 as set forth by the examiner, as well as one of 216.

Applicants in that paper also cited *In re Deuel*, 34 USPQ2d 1210, 1215. That case did not involve the question of whether a genus rendered its individual species obvious. Applicants also cited *In re Baird*, 29 USPQ2d 1550, 1552. But as the Court noted, the reference had "a broad range of variables". Specifically, there was R, R', R", n1, n2, X and X'. And many of these were defined rather broadly. For example, "R is selected from substituted and unsubstituted alkylene radicals of from about 2 to about 12 carbon atoms, alkylidene radicals of from 1 to 12 carbon atoms and cycloalkylidene radicals of from 3 to 12 carbon atoms". The genus of the reference encompassed billions if not trillions of compounds.

With regard to applicants' point in the first full paragraph of page 4 of the remarks of that paper, the examiner was not saying that the monovalinate had been prepared. If it had been, the reference would be an anticipation. Rather, this was to rebut applicants argument about alleged "difficulties" in preparing a mono ester. The examiner's point is that in Example 6, even though the diester was the intended product, some mono-ester was prepared anyhow. This rebuts the notion that there are

such terrible difficulties in preparing a mono ester, because, in fact, an mono ester appeared as a byproduct in an actual synthesis of the diester.

Claims 23-29 are rejected as obvious, 35 U.S.C. 103 from Verheyden in view of Beauchamp (1992).

The claimed species is the monovalinate ester of Ganciclovir, as the HCl salt. The reference teaches Ganciclovir, and the HCl salt is named at column 2, line 64.

With regard to the CMV of claims 25-26, note column 3, line 16 which names CMV. Human use for claim 28 is disclosed at column 3, line 35. The oral administration of claims 24 and 27 is exemplified in example 4D in column 8, lines 55-68 and also at column 3, lines 37-47. With regard to the physical characteristics recited in claim 29, note the discussion in the above rejection.

Ganciclovir is extremely similar in structure to Acyclovir. Their structures are indeed identical, except that Acyclovir has one hydroxy methyl attached to the methoxy methyl side chain and Ganciclovir has two. Both are antivirals used to treat herpes infections. Hence, one skilled in the art would find it reasonable to infer information from one about the other. The difference is so small (one hydroxymethyl versus two) that if these are not analogous, then what is? The entire rest of the molecule, as well as the utility, is the same. A secondary reference is always going to have some structural difference, otherwise the secondary reference will itself anticipate.

Beauchamp (1992) teaches that of all the amino acid prodrugs tested with Acyclovir, the L-valyl ester "was the best prodrug". It gave 63% urine availability as opposed to 19% for the non-esterified drug. One skilled in the art would be motivated to obtain this enormous improvement with Ganciclovir too by preparing the L-valyl ester

of ganciclovir in order to obtain a comparable improvement. Thus, the secondary reference provides abundant motivation to prepare this exact L-valyl ester.

Further with regard to hydrochloride, Method A of the secondary reference gave the salts as hydrochlorides (see page 159, column. 1, 14th from last line).

The traverse, presented in the parent, paper of 8/13/02, was unpersuasive. The question of whether Acyclovir and Ganciclovir have the exact same profile of actions, or whether adenosine and Psicofuranine have different properties is not the point. The only issue here is whether the Beauchamp (1992)'s teaching that it is extremely advantageous to convert Acyclovir to its valinate ester would motivate one of ordinary skill in the art to do the same for a compound (Ganciclovir) of very similar structure and identical utility. Even the Crumpacker reference cited by applicants calls Acyclovir an "analogue" of Ganciclovir (page 721, column 1 second full paragraph). Moreover, the antiviral mechanism of the two drugs is the same. As Crumpacker teaches, both drugs are converted to the triphosphate, and that triphosphate is, in both cases, an inhibitor of CMV DNA polymerase. The fact that Ganciclovir is not also "an absolute chain terminator" hardly prevents these two references from being combinable.

Next, applicants argued in that paper that applying the teaching of the secondary reference would give the bis ester, rather than the mono ester. The bis-ester is probably also obvious, but that is not the issue here, only whether the mono-ester would be obvious. The fact that the bis-ester is obvious does not make the mono-ester non-obvious. The compounds of Beauchamp (1992) are all monoesters, so one simply cannot argue that monoesters are not an obvious form.

In the above, the discussion of arguments made in the parent was done for completeness of record. If applicants wish to rely on such arguments in this case, they must actually present such arguments. Applicants are of course not obliged to rely in this case on arguments made in the parent.

The remarks submitted with this application refer to 5 documents "to be made of record". As for the Susan Malcolm declaration, it is unclear what use, if any, applicants intend for this document, which was not discussed at all in the parent, and which was submitted in the context of claims which are not the same as those presently under prosecution. At any rate, the examiner would stand by remarks made in the second Examiner's Answer in the grandparent case:

> Appellants also refer to the Malcolm declaration. Appellants have presented three sets of data: The material in the specification, material in a "Memorandum of Record" submitted with the Reply Brief, and material in the Malcolm declaration, all different. Specifically, it is not clear why the Malcolm data is different from the data presented previously in the "Memorandum of Record". Three out of the five reported numbers are different, and all the Standard Deviations are different.
>
> The second Appeal Brief, page 11, addresses this difference, but the answers are not very specific. The remarks refer, for example to "recalculations based on purity analysis of the materials tested between the preliminary and final data reporting." It is hard to know what to make of this. Does this mean that the test was run, and then a purity analysis was performed, and the purity was not what was thought, so that the numbers were recalculated?
> If so, such things ought to be in the declaration, not in the remarks. The Malcolm declaration says nothing at all about purity, so one would assume that the materials tested were completely pure.
>
> Further, the data shows expected, not unexpected differences. Acyclovir monovalinate has 53.4% bioavailability; the corresponding claimed Ganciclovir monovalinate has 55.4%. Given the fact that the exact numbers that are obtained are a rather sensitive function of the exact details as to how the test is run (as declarant sets forth in paragraph 9), such a difference is hardly meaningful. Preparing the Acyclovir valinate puts it into a form where about half is bioavailable; the same has now been found true for the claimed Ganciclovir monovalinate. One would expect from the Acyclovir results just what was actually found, and hence no unexpected results are seen. The declarant notes the 1.6 ratio between the Ganciclovir mono- and di-esters of Ganciclovir (up from the 1.5 ratio seen in the "Memorandum of Record") However, as the examiner has repeatedly pointed out in the prosecution of this case, this rejection is not over the bisvalinate.

The Maag, Dvorak and Han declarations are notd, but these go to the issue of crystallinity, not relevant in this case. The 5th item is of unclear relevance, and is cited on the PTO-1449.9

Specification

The amendment to page 1 of the specification is objected to as new matter. The last sentence incorporates disclosures from 08/281893, of which this case is a CIP. It introduces new matter to include any material that was in that case which was not carried forward from that case into 08/453223.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 23-29 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-6 of U.S. Patent No. 6083953. Although the conflicting claims are not identical, they are not patentably distinct from each other because the current claims are just a slightly broader versions of the claims in 6083953. Claim 23 covers both the amorphous and crystalline forms of the salts. The examiner notes that a Terminal Disclaimer was filed in the parent, but that does not carry through to the daughter case; a fresh one must be filed.

This is a continuation of applicant's earlier Application No. 09903221. All claims are drawn to the same invention claimed in the earlier application and could have been

finally rejected on the grounds and art of record in the next Office action if they had been entered in the earlier application. Accordingly, THIS ACTION IS MADE FINAL even though it is a first action in this case. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no, however, event will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mark L. Berch whose telephone number is 571-272-0663. The examiner can normally be reached on M-F 7:15 - 3:45.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mukund Shah can be reached on (571)272-0674. If you are unable to reach Dr. Shah within a 24 hour period, please contact James O. Wilson, Acting-SPE of 1624 at 571-272-0661. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306 for regular communications and (703) 872-9306 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0198.

Mark L. Berch
Primary Examiner
Art Unit 1624

March 11, 2004